

REVIEW

Resection margins and R1 rates in pancreatic cancer – are we there yet?

C S Verbeke

Department of Histopathology, St James's University Hospital, Leeds, UK

Verbeke C S

(2008) *Histopathology* 52, 787–796

Resection margins and R1 rates in pancreatic cancer – are we there yet?

The prognosis of pancreatic cancer is poor, even for those patients who undergo surgical resection. The rate of local recurrence is high, despite the fact that in most series complete ('R0') resection is reported to be achieved in the majority of patients. The discrepancy between pathological assessment and clinical outcome indicates that microscopic margin involvement (R1) is

frequently underreported, and potential causes for this are discussed in this review. Special emphasis is given to the variation that exists between currently used dissection techniques and their impact on the assessment of the resection margins in pancreatoduodenectomy specimens.

Keywords: cancer, pancreas, pathology, resection margin

Abbreviations: CRM, circumferential resection margin; JPS, Japan Pancreas Society; PDE, pancreatoduodenectomy; RM, resection margin; R0, complete resection; R1, microscopic margin involvement; SM, superior mesenteric; UICC, International Union Against Cancer

Introduction

The prognosis for patients with ductal adenocarcinoma of the pancreas is poor.¹ Most patients present with advanced disease, resulting in resection rates of just over 10%. Even in patients who undergo pancreatic resection, tumour recurrence is frequent and 5-year survival amounts to only 7–25%.²

Resection margin (RM) involvement is generally believed to be critical to survival in pancreatic cancer.^{3–7} However, the rates of microscopic margin involvement (R1) reported in the literature vary markedly, from as low as 16% to >75%, and correlation with clinical outcome is observed in some, but not all studies.^{8–18}

Whereas the occurrence and prognostic significance of margin involvement have been well recognized in rectal and oesophageal cancer,^{19–22} assessment of the RM status in pancreatic cancer has been neglected.

Address for correspondence: Dr C S Verbeke, Department of Histopathology, St James's University Hospital, Beckett Street, Leeds LS9 7TF, UK. e-mail: caroline.verbeke@leedsth.nhs.uk

Only recently has there been an increasing interest in the involvement of RMs in pancreatic cancer and its prognostic implications.

The reason for the wide variation in reported R1 rates lies in the lack of international consensus regarding fundamental issues such as the definition of microscopic margin involvement, the definition of what exactly constitutes the circumferential resection margin (CRM) in pancreatoduodenectomy specimens (PDEs), and a standardized protocol for the pathological examination of these specimens. Confusing nomenclature and problems in distinguishing between pancreatic, ampullary and distal bile duct cancer are further compounding factors.

We are currently in a period of transition, in which the quality of pathology reporting of PDEs has not yet reached the level of standardization and optimization that has become established for the surgical procedure.²³ Quality assessment and quality assurance, two important issues in modern diagnostic pathology, are addressed in different ways and need further development and standardization.

Resection margins in pancreatoduodenectomy specimens

It is remarkable that despite the existence of a considerable body of literature on the incidence and prognostic significance of RM involvement in PDEs, there is currently no consensus on what exactly constitutes the CRM in these specimens. Although the transection margins of the pancreatic neck, the distal bile duct and the duodenum and/or stomach are readily identified, there exists controversy over which, if not all, parts of the surface of the pancreatic head are to be included in the CRM assessment.

Based on anatomical considerations, it seems sensible to distinguish between an anterior and a posterior surface, which are separated by the medial CRM, the part of the surface of the pancreatic head that faces the superior mesenteric (SM) vessels (Figure 1). The posterior CRM is generally believed to be most frequently involved, therefore requiring careful assessment.^{17,24–26} It is sometimes also referred to as the ‘retroperitoneal CRM’, which is a misnomer, as the entire head of pancreas, not just this surface, is located in the retroperitoneum.

The anterior surface is not a true RM, because the surgeon does not transect any tissues in this area. Although it is not a CRM as such, the presence of tumour cells at the anterior surface is likely to increase the risk of local tumour recurrence,^{27,28} and it is therefore appropriate to include this surface in the assessment of the CRM. In some pancreatic cancer centres in the UK and continental Europe, the anterior surface has now been included in the examination protocol.²⁹ In Japan, it has been an integral part of the Japan Pancreas Society (JPS) classification for many years.³⁰ In contrast, in the USA the notion of the

anterior surface or margin has been introduced only recently.³¹ In practice, however, the anterior surface is not routinely examined, and in many US centres RM assessment is limited to the pancreatic and bile duct transection margins and the medial CRM or ‘uncinate margin’.^{18–33} The latter term is confusing, since it is mainly used as synonymous with the medial CRM, but occasionally refers to a true transection margin, produced by the surgeon when dividing the uncinate process as close to the SM artery as possible.^{33,34} With current standardized surgical procedures, however, the uncinate process remains intact and dissection of the SM artery is performed in the soft tissue plane, which corresponds to the medial CRM of the specimen.

The medial CRM has a shallow groove-like shape, and although the width and depth of the groove may vary, it is readily identified as it runs from the inferior to the superior border of the pancreatic head in a slightly curved fashion, passing underneath and behind the transected pancreatic neck. Its surface is usually slightly glistening, and its borders are often flanked by rows of clips or ties on small veins that drain from the pancreatic head into the SM vein (Figure 2). It is on this surface that segments of the SM vein, portal vein or SM artery are to be found, if the cancer is adherent to the major vessels, necessitating vascular resection. The resected vascular portion may either be a true tubular structure, or, more commonly, a small oval ‘patch’ of vessel wall attached to the superior mesenteric vein groove, which can be easily overlooked by the unwary (Figure 3).

Microscopic margin involvement

In addition to the controversies over which surfaces constitute the CRM, there is also lack of consensus

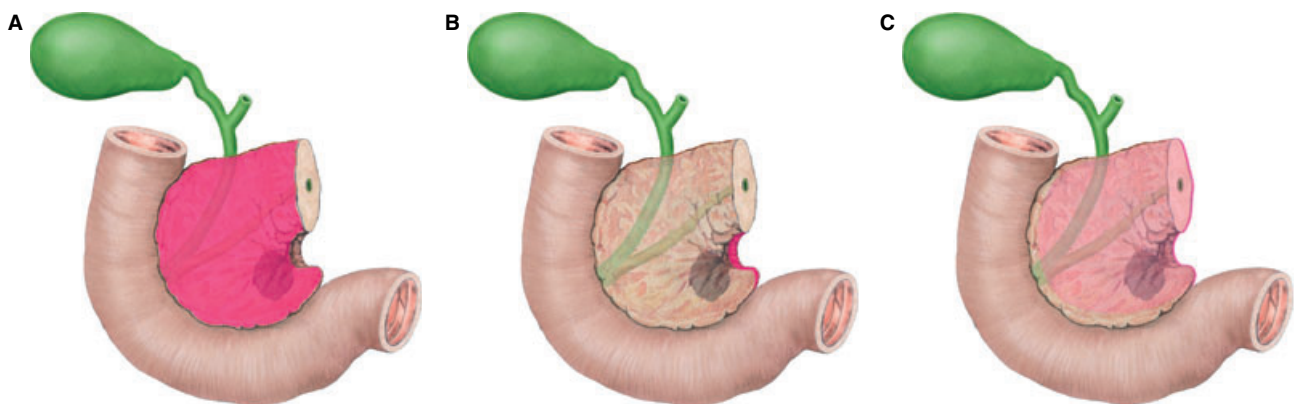


Figure 1. The circumferential resection margin in pancreatoduodenectomy specimens consists of the anterior surface (A), the medial margin (B) and the posterior margin (C).

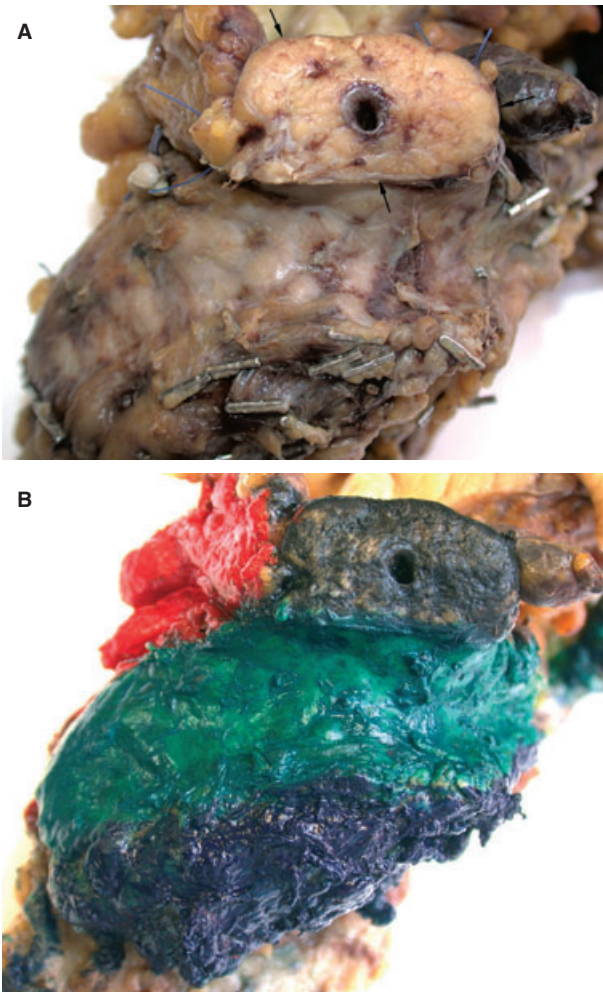


Figure 2. View on the medial aspect of a pancreatoduodenectomy specimen. **A**, The superior mesenteric vein (SMV) groove consists of a shallow, smooth surface, which curves behind the transection margin of the pancreatic neck (arrows). The SMV groove is often flanked by clips on small veins that drain from the pancreatic head into the SMV. **B**, Multicolour inking of the specimen clearly identifies the SMV groove or medial circumferential resection margin (CRM; green), which runs behind the pancreatic transection margin (black) and separates the anterior surface (red) from the posterior CRM (blue).

regarding the definition of microscopic margin involvement (R1). Again, approaches differ worldwide. In the USA, many pathologists consider a margin positive if tumour cells are present at the surface of the RM.^{18,31,33} In Europe, the R1 definition may vary, but most pathologists regard a RM as involved if tumour is present within 1 mm of the margin.

The '1 mm rule', as it is commonly used in the UK,²⁹ is a mere adoption of the R1 definition used for the reporting of rectal cancer. Several large studies based on careful correlation between the clinical outcome of rectal cancer patients and the exact measurement of

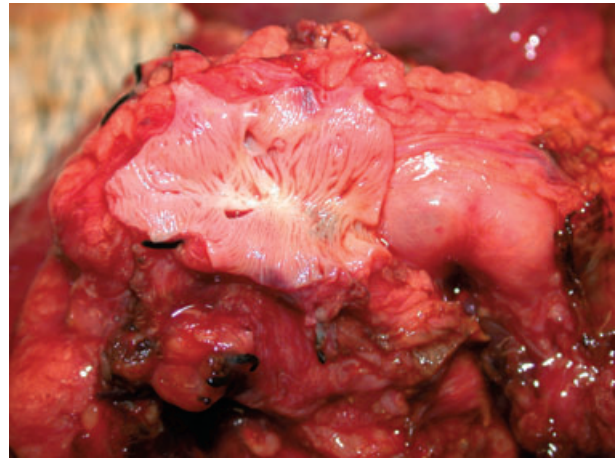


Figure 3. An irregular portion of the wall of the superior mesenteric vein is tightly tethered to the medial circumferential resection margin.

the minimum distance between the infiltrating tumour and the mesorectal RM have demonstrated a strong correlation between a clearance of ≤ 1 mm and local recurrence.^{35,36} Unlike rectal cancer, the R1 definition has never been validated for pancreatic (or indeed ampullary or distal bile duct) cancer.

It is important to remember what 'R1' exactly stands for. According to the International Union Against Cancer (UICC) classification, it is defined as 'presence of residual tumour after treatment'.³⁷ Whether tumour cells are left behind in the surgical bed is of course not directly assessable, and can be determined only by inference from what is observed at the RM of the surgical specimen. At this point it is evident that the pattern of tumour growth is to be considered. Absence of tumour cells at or within 1 mm to the specimen surface is less likely to indicate complete resection, i.e. absence of tumour beyond the line of resection, if the tumour growth pattern is dispersed rather than compact. One of the characteristic features of pancreato-biliary-type adenocarcinoma is its so-called infiltrative growth pattern, which refers to a dispersed and discontinuous tumour growth and has been linked to the aggressive biological behaviour and poor clinical outcome of pancreatic cancer.

Based on these considerations, the currently used R1 definition needs to be revised for the reporting of pancreatic ductal adenocarcinoma, and a clearance >1 mm may be found more appropriate. The '0 mm clearance' definition, as it is commonly used in the USA and Canada, is likely to underestimate the presence of residual tumour in the surgical bed. It may, however, be considered for the assessment of the anterior CRM, since this is a tissue surface rather than a resection

plane. Ultimately, only through careful correlation of meticulously recorded microscopic findings at the resection margin with local tumour recurrence, similar to the commendable studies on rectal cancer, can an R1 definition specific for pancreatic cancer be established. For the data of such studies to be compared among (inter)national centres, the pathological work-up of PDEs should be fully standardized. Unfortunately, this is currently not the case.

Gross specimen examination

The development of guidelines for the macroscopic examination of PDEs has lagged behind that for other gastrointestinal cancers. This is in part due to the fact that pancreatic cancer surgery is performed in a relatively small number of specialized centres and hence only a minority of diagnostic pathologists are confronted with these specimens. Furthermore, in view of the extremely poor prognosis of pancreatic cancer, clinicians sometimes tended to adopt a rather nihilistic approach to the treatment of these patients, and expressed limited interest in a pathology report providing data, including the RM status, that would be considered essential for other gastrointestinal cancers.

Fortunately, in the past few years, major improvement has been achieved surgically in terms of postoperative morbidity and mortality, and refinement and standardization of technical procedures.^{2,23} Significant progress has also been made in preoperative imaging, with diverse modalities enabling the establishment of well-defined criteria for selection of patients eligible for surgery.³⁸

So far, histopathology has failed to follow suit, and a wide range of different dissection techniques are currently used, many of which are based on tradition rather than evidence-based rationale. Despite appeals for standardization,^{25,26,32,39} there is currently no consensus on specimen handling, and guidelines issued by the pathology professional bodies in the UK and USA lack detailed guidance on the assessment of the RMs.^{24,29,40}

SPECIMEN ORIENTATION AND INKING

The first step of any pathology protocol for the dissection of PDEs should be the multicolour inking of the relevant surfaces (Figure 2B). Colour-coded inking is helpful in identifying the different parts of the CRM (anterior, posterior and medial), both while handling the specimen slices and during microscopic examination, and allows accurate recognition of exactly which CRM is involved.

SPECIMEN DISSECTION

Longitudinal opening of the main pancreatic duct and common bile duct has traditionally been the preferred dissection method. From a practical point of view it is, however, often a difficult undertaking to open these small ducts, which are located within the several centimetres wide pancreatic head and often distorted or obstructed by tumour. This technique is also of limited value for the assessment of the RMs, tumour origin and tumour extension. Opening of the ducts disrupts the specimen surface along two tracks that run across the entire head of pancreas. This interferes with accurate evaluation of the CRM. As the common bile duct traverses the pancreatic head posteriorly, it is usually opened through the posterior surface, hence disrupting that part of the CRM that is frequently involved.^{8,17,24–26,39,41,42} Opening of the main pancreatic duct appears particularly uninformative in specimens harbouring a solid tumour. Since 'ductal' adenocarcinoma of the pancreas, outside the context of intraductal papillary-mucinous neoplasia, does not arise from the main pancreatic duct,⁴³ tumour involvement of the duct offers no clues regarding the cancer origin. Finally, evaluation of the extent of the tumour requires further specimen dissection in addition to the longitudinal opening of the ducts, and it is at this point that slicing in one plane or another is used.

Bivalve or multivalve slicing (Figure 4) is not easy to perform, not least because it involves longitudinal sectioning of the duodenal wall. Consequently, the slices are usually relatively thick and few in number, thereby limiting views on the tumour, key anatomical structures and CRM. Since the resulting specimen slices are large, this dissection technique is usually followed by slicing in another plane, often one perpendicular to the posterior surface to allow inspection of this CRM.³⁹ These combined dissection procedures result in a large number of tissue slices and fragments, which vary in size and are cut in different planes. Three-dimensional reconstruction of the findings and measurement of the tumour are often difficult for the examining pathologist and even more so for pathologists or surgeons when (re-)viewing the slides or pictures taken at the time of specimen dissection.

Slicing perpendicular to the main pancreatic duct or so-called bread loaf slicing (Figure 5), as recommended by some,³¹ produces an adequate number of thin slices. However, slicing of the pancreas becomes difficult when approaching the duodenal wall in a tangential plane, and demonstration of key anatomical structures such as the ampulla, distal pancreatic duct and bile duct may be suboptimal. Slicing perpendicular to an

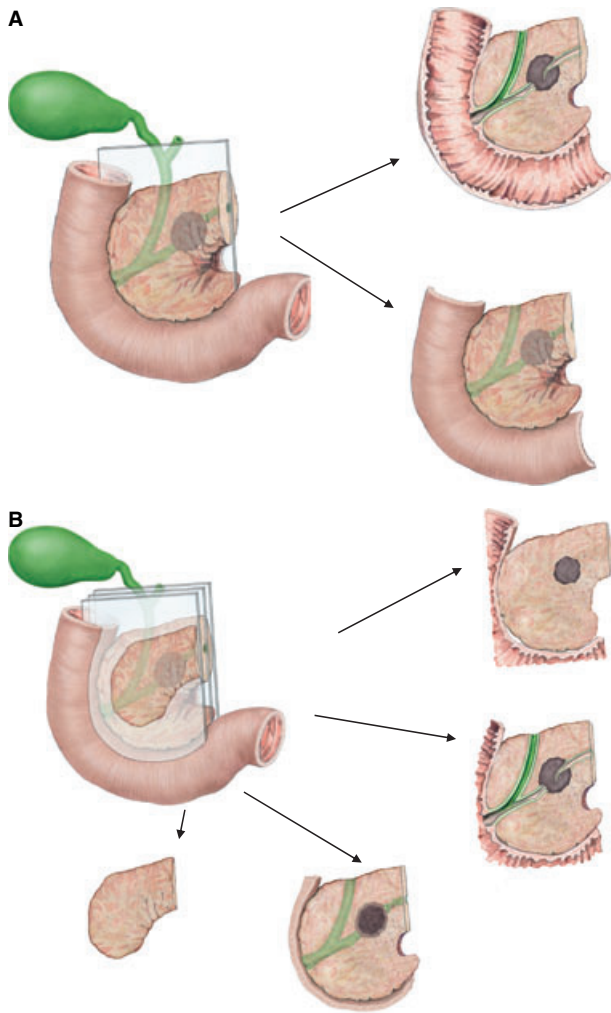


Figure 4. Slicing of pancreatoduodenectomy specimens. A, Bivalve slicing of the pancreatic head, ideally performed in the plane of the pancreatic and common bile duct, produces two large and thick tissue slices. B, Multivalve slicing results in a larger but still limited number of specimen slices that usually require further dissection to allow sampling of standard tissue blocks.

axis that follows the curvature of the pancreatic head, as advocated by the JPS,³⁰ solves the latter problem, but has the disadvantage of continuous alteration in the planes of section as slicing is followed along that curved axis.

In recent years, a novel dissection technique has been increasingly used in European and UK pancreatic cancer centres. It is based on serial slicing of the entire pancreatic head in a single axial plane, i.e. perpendicular to the longitudinal axis of the duodenum (Figure 6). It does not prescribe opening of the pancreatic or bile duct, hence the CRM remains intact. This technique has several obvious advantages. It is simple and easy to perform, and can be used independent of

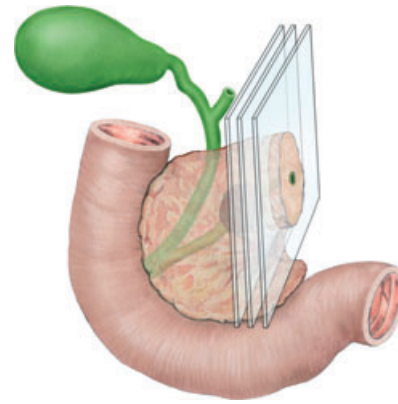


Figure 5. Slicing perpendicular to the main pancreatic duct delivers an adequate number of slices of varying width. If slicing is performed in the same plane throughout the entire pancreatic head, problems may arise when reaching the ampulla and duodenal wall.

the location and nature of the pathology. A large number of slices is produced – usually between 10 and 13 – allowing extensive views of the lesion and its relation to the entire CRM and key anatomical structures, which are consistently present in slices from specific dissection levels.¹⁷

TISSUE SAMPLING

At the time of gross examination, it is often difficult to appreciate whether the CRM is involved by tumour. Unlike in large bowel cancer, where the invasive tumour front is usually well-defined and readily identifiable, the periphery of pancreatic head cancers, in particular pancreatic and distal bile duct adenocarcinoma, is obscured by fibrosis and inflammatory changes associated with so-called obstructive pancreatitis that is present in the majority of cancer-bearing PDEs. The highly dispersed, discontinuous growth pattern of pancreatobiliary-type adenocarcinoma contributes to the difficulty in identifying macroscopically the boundaries of the tumour. As naked-eye inspection is not reliable in this respect, extensive tissue sampling from the tumour and adjacent CRM is required. Failure to do so will inevitably lead to underestimation of margin involvement. This is demonstrated by correlation of the R1 rate with the extent of sampling from the CRM.¹⁷ Further support for the importance of extensive tissue sampling comes from a study in which the detection of cancer cells in soft tissue around the superior mesenteric artery was compared between conventional histology and K-ras mutational analysis. In a considerable proportion (43%) of cases that were negative on histology but positive according to the

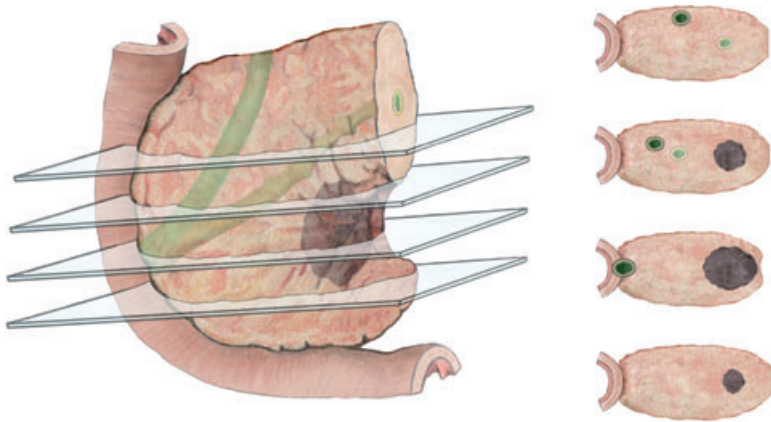


Figure 6. Slicing of the specimen in an axial plane is easy to perform as the duodenal wall is cut in a cross-sectional fashion. The technique produces a large number of specimen slices and provides good views of the tumour and its relationship to the key anatomical structures and the entire circumferential margin.

K-ras analysis, cancer cells were indeed identified when additional tissue sections were examined microscopically.⁴⁴

As discussed above, in American centres assessment of the CRM is often limited to the medial ('uncinate') CRM and based on a single full-face section,^{18,32} often performed intra-operatively as a frozen section.³³ This procedure not only limits examination to <20% of the entire CRM, but is wholly irrelevant if the tumour is located elsewhere in the pancreatic head, away from the medial CRM. In addition, full-face sectioning precludes exact measurement of the minimum distance from the tumour to the resection margin. Cutting deeper into the full-face tissue block may lead to overestimation, whereas too superficial sectioning may result in underestimation of margin involvement.³⁴

R1 rate and clinical outcome

As outlined above, considerable variation exists in the dissection and sampling techniques as well as in the definitions that are currently used to report the RM status in PDEs. It is likely that this non-standardized approach accounts at least in part for the wide variation in R1 rates – between 16% and 85% – that have been reported for ductal adenocarcinoma of the pancreas.^{6,8–18}

Critical review of survival data of pancreatic cancer patients reveals incongruence between the reported R1 rate and clinical outcome, even in series with, for this cancer, relatively large patient numbers. First, the local recurrence rate of pancreatic cancer after resection with curative intent is high – generally reported between 67% and 86%^{8,18,45,46} – and seems to be at odds with the R1 rate, which in the majority of published series lies well below 30–40%. Second, the overall survival figures in series with low R1 rates

do not differ significantly from those with higher R1 rates.^{2,17,47} Third, the difference in survival between patients who underwent an R0 resection and those with a R1 resection is usually small, typically between 4 and 8 months, and often statistically non-significant.^{6,10,18,42,48,49}

Interestingly, in two recent studies based on fully standardized pathological examination and the '1 mm rule' for margin involvement, the reported R1 rate for pancreatic ductal adenocarcinoma exceeded 70% and amounted to 85%.^{17,50} Despite the unusually high R1 rate, the overall survival was similar to that reported previously in series with significantly lower rates of RM involvement. In addition, although the number of R0 resections was very small, the median survival of this subgroup was significantly better than that of the R1 subgroup and amongst the highest reported in the literature so far.¹⁷ Although based on small numbers, the observations made in both studies raise several important issues. First, both used a nearly identical dissection technique that is based on serial axial slicing and differs in several key aspects from the traditional approach. This seems to indicate that the dissection and sampling technique has a significant impact on the assessment of the margin status in PDEs. Second, the examination protocol used in both studies was fully standardized, and the fact that the R1 rate in both studies reached a similar high value suggests that standardization is key to providing reproducible data. Third, the significant survival benefit of patients in the (small) R0 subgroup in one of the studies¹⁷ suggests that resection margin involvement is often underestimated, and hence, incorrect reporting of R0 resection results in blurring of the difference in outcome between the R0 and R1 subgroups.

Indirect support for the underestimation of RM involvement in most published series comes from a recent study that detected cells harbouring *K-ras*

mutation in 53% of pancreatic cancer specimens with histologically negative surgical margins. Although this study was limited in that it investigated only the pancreatic transection margin and 'retroperitoneal' CRM, it observed a highly significant survival difference between R0 and R1 cases based on molecular analysis (median 15 versus 55 months).⁵¹

Little is known about the relative frequency of involvement of the different resection margins in R1 resections and their significance as determinants for survival. The posterior and medial CRMs are affected most frequently (up to 66% of all R1 resections).^{17,52,53} Involvement of the anterior surface seems to be less frequent (22–26%),^{17,41} although correlation with 5-year survival has been reported.^{27,41} Involvement of two or more CRMs is observed in >40% of R1 cases.^{17,54} Involvement of the bile duct and pancreatic transection margins is usually considerably less frequent than that of the CRMs; however, this may reflect the use of intra-operative frozen section analysis.

R1 rate and tumour origin

The considerable variation in reported R1 rates in pancreatic ductal adenocarcinoma may to some extent also result from inaccuracies in determining the cancer origin. Indeed, the wide range of relative incidences that have been reported for pancreatic, ampullary and distal bile duct cancer in PDE series^{3,17,55–58} suggests that identification of the tumour origin is not always performed in the same way and with the same level of accuracy. In some studies, slide review has revealed misclassification of the tumour origin in up to 39% of adenocarcinomas arising in the pancreatic head.^{10,59} In addition, as identification of the tumour origin is based mainly on macroscopic findings, slide review is often not helpful in redressing this issue in retrospective studies. Yet, based on the limited number of studies that provide separate data for pancreatic, ampullary and bile duct cancer, the R1 rate differs significantly between the cancer groups.^{17,56–58,60} In general, margin involvement is observed more frequently in pancreatic than ampullary cancer, whereas the R1 rate in distal bile duct carcinoma appears to exceed that of ampullary and approach the R1 rate in pancreatic cancer.^{17,56,58,60} Significantly lower local recurrence rates in ampullary compared with pancreatic and bile duct cancer indirectly support these observations.^{61–63} Hence, failure to identify the exact tumour origin may influence the R1 rate, and inclusion of ampullary or distal bile duct adenocarcinomas in pancreatic cancer series can result in an incorrectly low R1 rate.¹

Further issues to be addressed

As discussed above, a universally accepted definition of microscopic tumour involvement that is predicated on the identification of the minimum tumour clearance specific for pancreatobiliary-type adenocarcinoma is a prerequisite for uniform reporting. This definition would, however, require further specification as to the mode of tumour propagation. In rectal cancer, involvement of the mesorectal CRM by the presence of lymph node metastasis within 1 mm of that margin proved to be associated with an increased risk of local recurrence. Although this risk was lower than that of margin involvement by direct tumour growth,^{20,64} it was considered sufficiently high for lymph node metastasis to be included in the R1 definition. Again, this part of the R1 definition for rectal cancer has, by want of validated guidelines specific for pancreatobiliary cancer, been adopted by many pathologists for the reporting of PDEs. The decision on whether lymph node metastasis should be included ultimately depends on the outcome of meticulous clinicopathological correlation in large multi-institutional studies that are based on a fully standardized examination procedure. The compilation of such evidence would take a considerable amount of time, and meanwhile this issue deserves conceptual consideration.

With the recent advances in imaging, detection of small adenocarcinomas of the ampulla or distal bile duct, measuring <1–2 cm in diameter, has become fairly common. Despite their small size and early T-stage, however, these tumours have often already spread to peripancreatic lymph nodes.^{65–67} Given the limited width of peripancreatic soft tissue included in PDEs, it is possible for such a positive lymph node to be present within 1 mm of the CRM. In such a scenario the margin would have to be reported as involved if lymph node metastasis was included in the R1 definition, despite complete excision of the small primary cancer. The surgeon faced with such a report might argue that completeness of surgical excision can only pertain to the local removal of cancer tissue and that this should not be extended to the assessment of tumour cells that have spread regionally. The UICC definition of the R-descriptor is rather unhelpful in this matter and specifies neither where the residual tumour cells are to be found (surgical bed, lymph node, nerve plexus, ...), nor what their mode of spread is or can be. Approaching this problem from a clinical perspective, the question of whether in this scenario the risk of local recurrence is increased is probably to be answered with a guarded 'yes'. However, following this line of thought, should tumour cells inside lymphatic

channels, perineural clefts or even blood vessels be reported as R1 if they are present within the appropriate distance of the CRM? This would dangerously blur the distinction between local, regional and distant tumour spread. Part of the confusion seems to be of a semantic nature. 'Residual disease' refers to both local and regional presence of residual tumour cells, and in clinical practice it can even include distant tumour spread. In contrast, 'complete surgical excision' is usually understood as local tumour clearance. A more precise definition of the R-descriptor would be helpful in clearing the current confusion.

The way forward

The major progress that has been made over the last 10–15 years in the reporting of rectal cancer has been highlighted throughout this review as a shining example of how meticulous pathology, careful clinicopathological correlation and optimized surgery allow evidence-based change of practice and, ultimately, improved patient care. Similar developments in pancreatic cancer have not yet been commenced, and a first important step would be the rigorous implementation of a fully standardized, detailed examination protocol. Quality assessment should be provided by review of macroscopic photodocumentation and microscopic slides during multidisciplinary case discussion and as part of multicentre studies. As a next step, based on data from standardized studies, benchmarks could be established against which to measure the quality of pathological data used for both diagnostic and scientific purposes.

Recent histological and molecular studies seem to indicate that resection margin involvement is significantly more frequent than commonly reported.^{17,44,50,51} This implies that pancreatic cancer represents for the majority of patients a locally advanced disease, which cannot be cured by surgery alone and requires adjuvant treatment. Future efforts will be focused on developing effective (neo-)adjuvant treatment modalities, and accurate and standardized pathology reporting should be in place to assess the effect of these new therapies.

Conclusions

Published data regarding the incidence of RM involvement and its clinical significance in terms of local recurrence and overall survival vary widely and do not allow definitive conclusions. The reasons for the variation in data are manifold and include the lack of consensus regarding the definition of microscopic

margin involvement, the use of confusing nomenclature for the CRMs, absence of a standardized dissection technique, variation in the extent and technique of tissue sampling, and difficulties in distinguishing between pancreatic, ampullary and distal bile duct cancer. Multicentre clinical trials are urgently needed to assess the impact of changes in patient management and use of new treatment modalities. However, without robust and reliable pathological data, these are unlikely to succeed in producing compelling evidence.

Acknowledgement

The author thanks Mr Paul Brown, Specialist Medical Illustrator, St James's University Hospital Leeds, for the colour drawings.

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